REMARKS

Applicant has canceled claims 2-5, 7-10, 12-13 and 14-22 to comport with the Restriction Requirement imposed by the Examiner in the last paper.

Applicant has amended claim 1 to specifically refer to the a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation to be a neurokinin-1 (NK-1) receptor antagonist, which has support in claim 4 as filed. Applicant has also canceled claim 4 as duplicative in view of the amendment to claim 1.

None of these amendments add new matter to the instant application.

Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 1, 4, 6 and 11 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,567,592 (Benet et al.) and International PCT Patent Publication No. WO 96/14845 (Hess). The Examiner asserts that Benet et al. "teaches the administration of a drug that is the particular cytochromes P450, CYP2D6 substrate which is a member of CYP family, in mediating oxidative biotransformation for the major clearance mechanism in humans" and that "CYP2D6 inhibitors such as quinidine, calcium channel blockers, and phenothiazines are useful bioenhancers to increase the bioavailability of a pharmaceutical compound through the inhibition of cytochrome P450." The Examiner also urges that Hess discloses the instant elected species which is an NK-1 receptor antagonist. The Examiner maintains that it "would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)-methylamino-piperidine as CYP2D6 in mediating oxidative biotransformation in combination with quinidine as a CYP2D6 inhibitor."

Applicants traverse. The combined use of an NK-1 receptor antagonist in combination with an inhibitor of CYP2D6 is not obvious in view of the cited references. There is no suggestion whatsoever in the prior art to use the claimed combinations. There must be some motivation or suggestion to make the claimed invention in light of the prior art teachings. *In re Brouwer*, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996).

The Examiner has acknowledged the novelty of the claimed combination as the "prior art does not disclose the employment of (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)-methylamino-piperidine as a CYP2D6 substrate in mediating

oxidative biotransformation in combination with quinidine as a CYP2D6 inhibitor." The Examiner should equally well acknowledge that there is no specific suggestion or motivation in the art to lead one to use this novel combination.

A specific suggestion in the art to combine the teachings and make the claimed invention is required to show obviousness. The Examiner has made parallels with other enzymes, *e.g.*, CYP3A, but other enzymes often play somewhat different roles in the metabolism of drug products and what is true for those enzymes (location, type and rate of metabolism of a drug), is not necessarily known to be true for the CYP2D6 enzyme, and especially not with respect to a specific class of drugs like the NK-1 receptor antagonists. Benet et al. only discuss the specific role of CYP3A enzymes and how to make drugs more bioavailable. However, the CYP3A enzyme, which appears to be present in all population groups, is different from the CYP2D6 enzyme, which is genetically variable and may be absent in some population groups. *see*, page 2 of specification. The problem solved by the present application to render all humans poor metabolizers such that serious drug-drug interactions do not occur. The nature of this problem is not at all suggested by the two cited references and cannot have led to the motivation to make the claimed combination.

There is no specific part of either of the cited references that would lead one of ordinary skill in the art to choose the specific invention claimed here. In the absence of a specific motivation in the art itself to combine the references and give one of ordinary skill a reasonable expectation of success, there can be no assertion of obviousness.

In view of the foregoing, Applicants respectfully request favorable reconsideration of the restriction requirement and allowance of the application.

Respectfully submitted,

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APPENDIX TO RESPONSE AND AMENDMENT
USSN 09/528,978

Amended claim 1.

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1. (Amended) A method of administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation and that is a neurokinin-1 (NK-1) receptor antagonist containing a primary, secondary or tertiary alkylamine moiety, or a pharmaceutically acceptable salt thereof, in combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, to a human in need of the intended pharmaceutical activity of such drug, wherein said drug and said CYP2D6 inhibitor are not the same compound.